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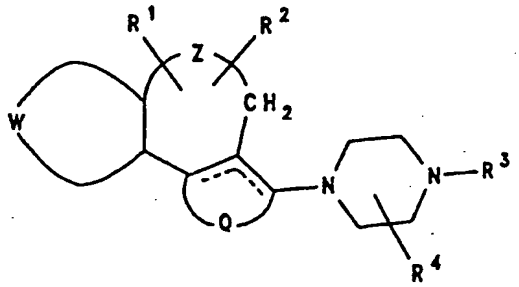
(54) Title: FUSED TRICYCLIC HETEROAROMATIC DERIVATIVES AS DOPAMINE RECEPTOR SUBTYPE LIGANDS

(57) Abstract

A class of fused tricyclic heteroaromatic compounds of formula (I), or a salt thereof or a prodrug thereof, containing a fused pyrazole, oxazole or pyrimidine ring are ligands for dopamine receptor subtypes within the body and are therefore of use in the treatment and/or prevention of disorders of the dopamine system, such as schizophrenia.



(I)

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FUSED TRICYCLIC HETEROAROMATIC DERIVATIVES AS DOPAMINE RECEPTOR SUBTYPE LIGANDS

This invention relates to a particular class of fused tricyclic heteroaromatic compounds based on a substituted isoxazole or pyrazole moiety. These compounds are ligands for dopamine receptor subtypes within the body and are therefore of use in the treatment and/or prevention of disorders of the dopamine system, including schizophrenia, depression, nausea, Parkinson's disease, tardive dyskinesias and extrapyramidal side-effects associated with treatment by conventional neuroleptic agents, neuroleptic malignant syndrome, and disorders of hypothalamic-pituitary function such as hyperprolactinaemia and amenorrhoea.

Upper gastrointestinal tract motility is believed to be under the control of the dopamine system. The compounds according to the present invention may thus be of use in the prevention and/or treatment of gastrointestinal disorders, and the facilitation of gastric emptying.

Dependence-inducing agents such as cocaine and amphetamine have been shown to interact with the dopamine system. Compounds capable of counteracting this effect, including the compounds in accordance with the present invention, may accordingly be of value in the prevention or reduction of dependence on a dependence-inducing agent.

Dopamine is known to be a peripheral vasodilator; for example, it has been shown to exert a dilatory effect on the renal vascular bed. This implies that the compounds of the present invention may be beneficial in controlling vascular blood flow.

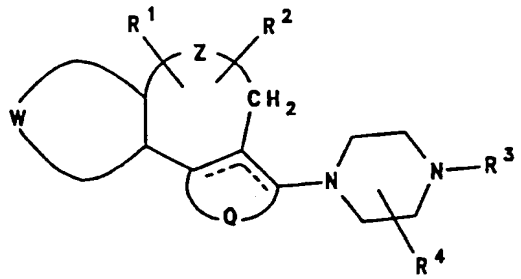
The localisation of dopamine receptor mRNA in rat heart and large vessels has been noted. This suggests a role for dopamine receptor ligands in

controlling cardiovascular function, either by affecting cardiac and smooth muscle contractility or by modulating the secretion of vasoactive substances. The compounds according to the present invention may therefore be of assistance in the prevention and/or treatment of such conditions as hypertension and congestive heart failure.

Molecular biological techniques have revealed the existence of several subtypes of the dopamine receptor. The dopamine D_1 receptor subtype has been shown to occur in at least two discrete forms. Two forms of the D_2 receptor subtype, and at least one form of the D_3 receptor subtype, have also been discovered. More recently, the D_4 (Van Tol et al., Nature (London), 1991, 350, 610) and D_5 (Sunahara et al., Nature (London), 1991, 350, 614) receptor subtypes have been described.

The compounds in accordance with the present invention, being ligands for dopamine receptor subtypes within the body, are accordingly of use in the treatment and/or prevention of disorders of the dopamine system.

The present invention accordingly provides a compound of formula I, or a salt thereof or a prodrug thereof:



(I)

wherein the broken line represents a double bond whereby the heteroaromatic ring containing Q is aromatic;

W represents the residue of an optionally substituted aromatic or heteroaromatic ring;

Q represents the residue of a heteroaromatic ring selected from $=N-NR^5-$, $-NR^5-N=$, $=N-O-$, $-O-N=$ and $=N-CR^6=N-$;

Z represents a chemical bond, an oxygen or sulphur atom, or a methylene or ethylene group;

R^1, R^2 and R^5 independently represent hydrogen or C_{1-6} alkyl;

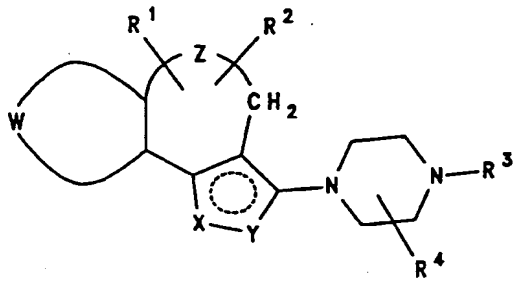
one of R^3 and R^4 represents hydrocarbon or a heterocyclic group, and the other of R^3 and R^4 represents hydrogen, hydrocarbon or a heterocyclic group; and

R^6 represents C_{1-6}alkyl or $-NR^aR^b$, in which R^a and R^b independently represent hydrogen or C_{1-6}alkyl.

The compounds of the present invention are preferably prepared and utilised in the form of the free base or as a pharmaceutically acceptable salt thereof.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

For the avoidance of doubt, it will be appreciated that the present invention relates to compounds of formula (IA), and salts and prodrugs thereof:



(IA)

wherein the broken circle represents two non-adjacent double bonds whereby the five-membered ring containing X and Y is aromatic;

W represents the residue of an optionally substituted aromatic or heteroaromatic ring;

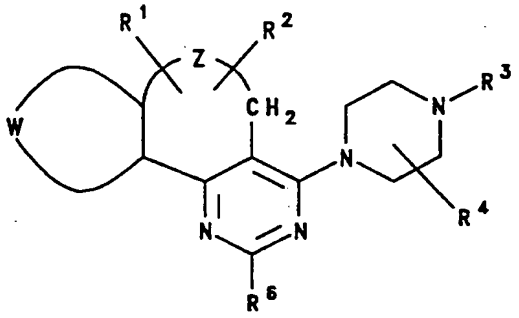
one of X and Y represents nitrogen, and the other of X and Y represents oxygen or N-R^5;

Z represents a chemical bond, an oxygen or sulphur atom, or a methylene or ethylene group;

R^1, R^2 and R^5 independently represent hydrogen or C_{1-6} alkyl; and

one of R^3 and R^4 represents hydrocarbon or a heterocyclic group, and the other of R^3 and R^4 represents hydrogen, hydrocarbon or a heterocyclic group.

The present invention also relates to compounds of formula (IB), and salts and prodrugs thereof:



(IB)

wherein

W represents the residue of an optionally substituted aromatic or heteroaromatic ring;

Z represents a chemical bond, an oxygen or sulphur atom, or a methylene or ethylene group;

R^1 and R^2 independently represent hydrogen or C_{1-6} alkyl;

one of R^3 and R^4 represents hydrocarbon or a heterocyclic group, and the other of R^3 and R^4 represents hydrogen, hydrocarbon or a heterocyclic group; and

R^6 represents C_{1-6} alkyl or $-NR^aR^b$, in which R^a and R^b independently represent hydrogen or C_{1-6} alkyl.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl and aryl(C_{1-6})alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably

linked through carbon. Examples of suitable heterocyclic groups include C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl and heteroaryl(C_{1-6})alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, isopropyl and t-butyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Particular aryl groups include phenyl and naphthyl.

Particular aryl(C_{1-6})alkyl groups include benzyl, naphthylmethyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, indolyl, aza-indolyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl(C_{1-6})alkyl groups include pyridylmethyl, pyrazinylmethyl, indolylmethyl and aza-indolylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C_{1-6} alkyl, adamantyl, phenyl, aryl(C_{1-6})alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, aryloxy, keto, C_{1-3} alkylenedioxy, nitro, cyano, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy, arylcarbonyloxy, C_{2-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, arylsulphonyl, trifluoromethanesulphonyloxy, $-NR^VR^W$, $-NR^VCOR^W$, $-NR^VCO_2R^W$, $-NR^VSO_2R^W$, $-CH_2NR^VSO_2R^W$, $-NHCONR^VR^W$, $-PO(OR^V)(OR^W)$, $-CONR^VR^W$, $-SO_2NR^VR^W$ and $-CH_2SO_2NR^VR^W$, in which R^V and R^W independently represent hydrogen, C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible <u>in vivo</u> into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The aromatic or heteroaromatic ring of which W is the residue is suitably a phenyl, naphthyl, furyl, thienyl, pyrrolyl or pyridyl ring, optionally substituted by one or more, preferably up to three, substituents. Examples of optional substituents on the aromatic or heteroaromatic ring of which W is the residue include halogen, trifluoromethyl, cyano, nitro, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy and C_{2-6} alkylcarbonyl.

Suitably, the aromatic or heteroaromatic ring of which W is the residue is unsubstituted. Where the ring is substituted, particular substituents include methyl, ethyl, isopropyl, methoxy, benzyloxy, fluoro and chloro.

Suitably, the substituents R^1 and R^2 independently represent hydrogen or methyl, especially hydrogen.

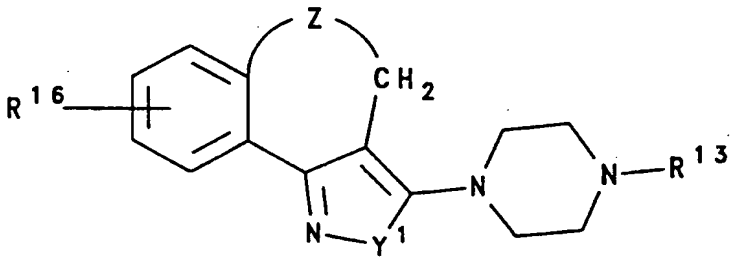
Suitable values for the substituents R^3 and R^4 include C_{2-6} alkenyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl and heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted. In addition, one of R^3 and/or R^4 may represent hydrogen. Examples of suitable substituents on the groups R^3 and/or R^4 include C_{1-6} alkyl, halogen, C_{1-6} alkoxy and nitro.

Particular values of R^3 and R^4 include hydrogen, allyl, cyclopropylmethyl, cyclohexylmethyl, benzyl, methyl-benzyl, chlorobenzyl, dichlorobenzyl, methoxy-benzyl, nitro-benzyl, naphthylmethyl, phenethyl, phenylpropyl and aza-indolylmethyl, provided that at least one of R^3 and R^4 is other than hydrogen. Suitably, one of R^3 and R^4 represents hydrogen, and the other of R^3 and R^4 is other than hydrogen. Preferably, R^4 represents hydrogen and R^3 is other than hydrogen.

Suitably, R^5 is hydrogen or methyl.

Suitable values for the substituent R^6 include C_{1-6} alkyl, amino, C_{1-6} alkylamino and di(C_{1-6})alkylamino. A particular value of R^6 is amino.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

Z is as defined with reference to formula I above;

Y^1 represents oxygen or N-R^{15};

R^{13} represents C_{2-6} alkenyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted;

R^{15} represents hydrogen or C_{1-6} alkyl; and

R^{16} represents hydrogen, halogen, trifluoromethyl, cyano, nitro, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or C_{2-6} alkylcarbonyl.

Examples of suitable substituents on the group R^{13} include one or more of C_{1-6} alkyl, halogen, C_{1-6} alkoxy and nitro.

Particular values of R^{13} with reference to formula IIA above include allyl, cyclopropylmethyl, cyclohexylmethyl, benzyl, methyl-benzyl, chlorobenzyl, dichlorobenzyl, methoxy-benzyl, nitro-benzyl,

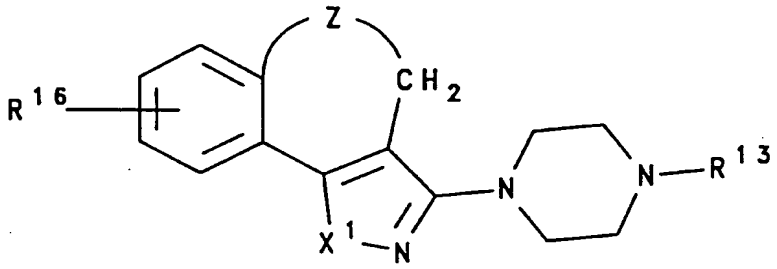
naphthylmethyl, phenethyl, phenylpropyl and aza-indolylmethyl.

Particular values of Y^1 with reference to formula IIA above include oxygen, NH and N-methyl.

Suitably, R^{15} is hydrogen or methyl.

Particular values of R^{16} include hydrogen, methyl, ethyl, isopropyl, methoxy, benzyloxy, fluoro and chloro, especially hydrogen.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof:



(IIB)

wherein

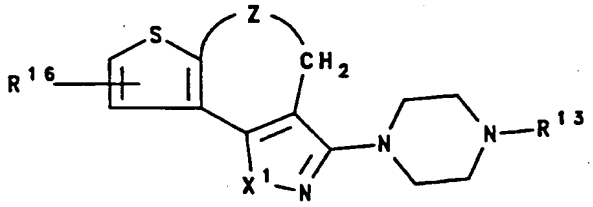
X^1 represents oxygen or N-R^{15};

Z is as defined with reference to formula I above; and

R^{13}, R^{15} and R^{16} are as defined with reference to formula IIA above.

Particular values of X^1 include oxygen, NH and N-methyl.

A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and salts and prodrugs thereof:



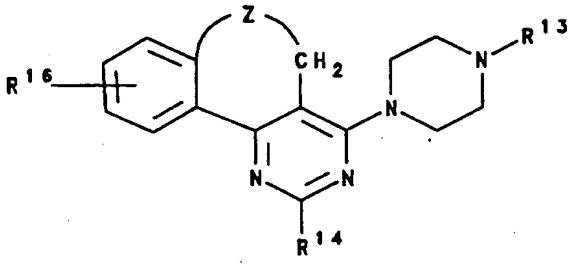
(IIC)

wherein

Z is as defined with reference to formula I above; and

X^1, R^{13} and R^{16} are as defined with reference to formula IIA above.

Another particular sub-class of compounds according to the invention is represented by the compounds of formula IID, and salts and prodrugs thereof:



(IID)

wherein

Z is as defined with reference to formula I above;

R^{13} represents C_{2-6} alkenyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted;

R^{14} represents C_{1-6} alkyl, amino, C_{1-6} alkylamino or di(C_{1-6})alkylamino; and

R^{16} represents hydrogen, halogen, trifluoromethyl, cyano, nitro, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or C_{2-6} alkylcarbonyl.

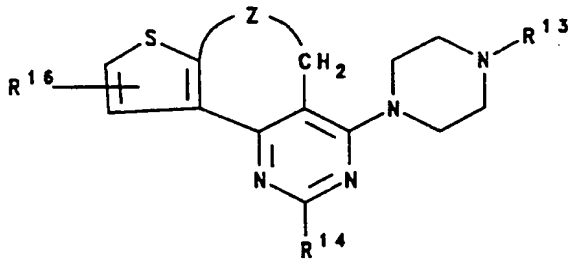
Examples of suitable substituents on the group R^{13} include one or more of C_{1-6} alkyl, halogen, C_{1-6} alkoxy and nitro.

Particular values of R^{13} with reference to formula IID above include allyl, cyclopropylmethyl, cyclohexylmethyl, benzyl, methyl-benzyl, chlorobenzyl, dichlorobenzyl, methoxy-benzyl, nitro-benzyl, naphthylmethyl, phenethyl, phenylpropyl and aza-indolylmethyl.

A particular value of R^{14} is amino.

Particular values of R^{16} include hydrogen, methyl, ethyl, isopropyl, methoxy, benzyloxy, fluoro and chloro, especially hydrogen.

A further sub-class of compounds according to the invention is represented by the compounds of formula IIE, and salts and prodrugs thereof:



(IIE)

wherein

Z is as defined with reference to formula I above; and

R^{13}, R^{14} and R^{16} are as defined with reference to formula IID above.

Specific compounds within the scope of the present invention include:

3-[4-(2-phenylethyl)piperazin-1-yl]-4,5-dihydro-1H-benzo[g]indazole;

3-(4-benzylpiperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole;

3-[4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)piperazin-1-yl]-4,5-dihydro-1H-benzo[g]indazole;

3-(4-benzylpiperazin-1-yl)-4,5-dihydronaphth[1,2-c]-isoxazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-4,5-dihydronaphth[1,2-c]isoxazole;

3-[4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)piperazin-1-yl]-4,5-dihydronaphth[1,2-c]isoxazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-4,5-dihydro-2-methyl-2H-benzo[g]indazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-4,5-dihydro-1-methyl-1H-benzo[g]indazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-4,5-dihydro-1H-thieno[2,3-g]indazole;

3-(4-benzylpiperazin-1-yl)-1,4-dihydroindeno[1,2-c]pyrazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-1,4-dihydroindeno[1,2-c]pyrazole;

3-(4-benzylpiperazin-1-yl)-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole;

3-[4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)piperazin-1-yl]-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole;

4-(4-benzylpiperazin-1-yl)-5H-indeno[1,2-d]pyrimidin-2-ylamine;

4-[4-(2-phenylethyl)piperazin-1-yl]-5H-indeno[1,2-d]pyrimidin-2-ylamine;

and salts and prodrugs thereof.

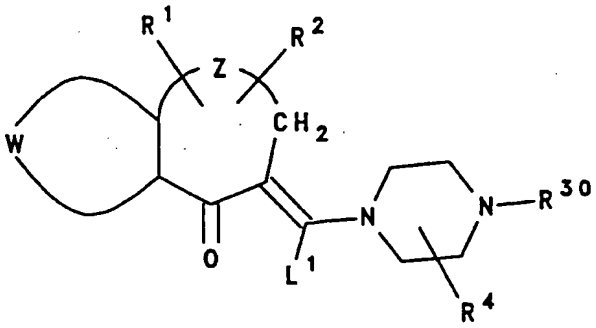
The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of

prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of disorders of the dopamine system, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds in accordance with the present invention, wherein Q represents $=N-NR^5-$, $-NR^5-N=$, $=N-O-$ or $-O-N=$, may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IVa:



(III)

H_2N-X^aH

(IVa)

wherein W, Z, R^1, R^2 and R^4 are as defined above, R^{30} corresponds to the group R^3 as defined above or represents an amino-protecting group, X^a represents oxygen or $N-R^5$ in which R^5 is as defined above, and L^1 represents a suitable leaving group; followed, where necessary, by removal of the amino-protecting group R^{30}; and subsequently, if required, attachment of the substituent R^3 by conventional means.

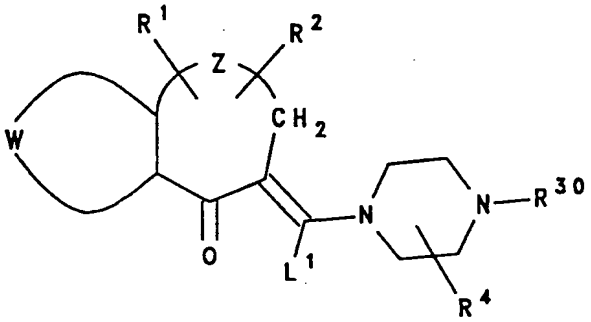
The reaction is conveniently carried out by stirring the reactants in a suitable solvent, for example a C_{1-4} alkanol such as ethanol or a mixture of N,N-dimethylformamide and methanol, optionally in the presence of a non-nucleophilic base such as ethyldiisopropylamine, suitably at room temperature.

Where the substituent R^{30} represents an amino-protecting group, this group is suitably an acyl moiety such as t-butoxycarbonyl (BOC), which can conveniently be removed as necessary by treatment under acidic conditions, e.g. stirring in trifluoroacetic acid.

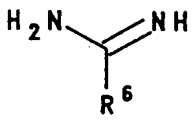
As will be appreciated, the overall reaction between compounds III and IVa will often give rise to a mixture of isomeric products of formula I, in one of which Q represents $=N-NR^5-$ or $=N-O-$, and in the other of which Q represents $-NR^5-N=$ or $-O-N=$. For this reason, it will generally be necessary at an appropriate stage to

separate the mixture of isomers obtained therefrom by conventional methods such as column chromatography.

The compounds in accordance with the present invention, wherein Q represents $=N-CR^6=N-$ may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IVb:



(III)



(IVb)

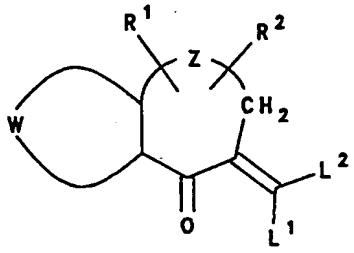
wherein W, Z, R^1, R^2, R^4 and R^6 are as defined above, R^{30} corresponds to the group R^3 as defined above or represents an amino-protecting group, and L^1 represents a suitable leaving group; in the presence of a base; followed, where necessary, by removal of the amino-protecting group R^{30}; and subsequently, if required, attachment of the substituent R^3 by conventional means.

The reaction is conveniently carried out by heating the reactants in a suitable solvent, typically at the reflux temperature. The base employed will suitably be a C_{1-4} alkoxide salt, in which case the reaction is conveniently effected in the corresponding C_{1-4} alkanol as solvent. Typically, the reaction may be carried out in the presence of approximately two equivalents of sodium isopropoxide, utilising isopropanol as the solvent.

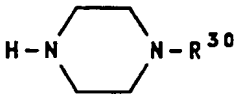
Where the substituent R^{30} represents an amino-protecting group, this group is suitably an acyl moiety such as t-butoxycarbonyl (BOC), which can conveniently be

removed as necessary by treatment under acidic conditions, e.g. stirring in trifluoroacetic acid.

The intermediates of formula III above may be prepared by reacting a compound of formula V with a compound of formula VI:



(V)



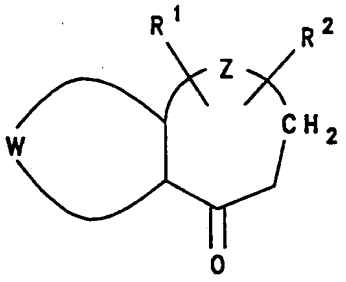
(VI)

wherein W, Z, R^1, R^2, R^{30} and L^1 are as defined above, and L^2 represents a suitable leaving group which may or may not be identical to L^1.

The reaction is conveniently effected by heating the reactants in an appropriate solvent, for example acetonitrile, suitably at the reflux temperature of the solvent employed.

The leaving groups L^1 and L^2, which may be the same or different, will suitably be conventional leaving groups well known from the art. For advantageous results, it has been found appropriate for L^1 and L^2 both to be C_{1-4} alkylthio groups, especially methylthio.

Where L^1 and L^2 both represent C_{1-4} alkylthio, the intermediates of formula V may be prepared by reacting a compound of formula VII:



(VII)

wherein W, Z, R^1 and R^2 are as defined above; with carbon disulphide and an appropriate C_{1-4} alkyl halide, e.g. methyl iodide, in the presence of a base such as sodium hydride.

The reaction is conveniently effected by stirring the reactants at room temperature in a suitable solvent, for example tetrahydrofuran.

Where they are not commercially available, the starting materials of formula VI and VII may be prepared by procedures analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art. For example, a compound of formula I wherein R^3 is hydrogen initially obtained may be converted into a compound of formula I wherein R^3 represents C_{1-6} alkyl by standard alkylation techniques, such as by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in N,N-dimethylformamide, or triethylamine in acetonitrile.

Where the above-described processes for the preparation of the compounds according to the invention

give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds useful in this invention potently inhibit [^{3}H]-spiperone binding to human dopamine D_4 receptor subtypes expressed in clonal cell lines.

[^{3}H]-Spiperone Binding Studies

Clonal cell lines expressing the human dopamine D_4 receptor subtype were harvested in PBS and then lysed in 10 mM Tris-HCl pH 7.4 buffer containing 5 mM $MgSO_4$ for

20 min on ice. Membranes were centrifuged at 50,000g for 15 min at 4°C and the resulting pellets resuspended in assay buffer (50 mM Tris-HCl pH 7.4 containing 5 mM EDTA, 1.5 mM $CaCl_2$, 5 mM $MgCl_2$, 5 mM KCl, 120 mM NaCl, and 0.1% ascorbic acid) at 20 mg/ml wet weight. Incubations were carried out for 60 min at room temperature (22°C) in the presence of 0.05-2 nM [^{3}H]-spiperone or 0.2 nM for displacement studies and were initiated by addition of 20-100 μg protein in a final assay volume of 0.5 ml. The incubation was terminated by rapid filtration over GF/B filters presoaked in 0.3% PEI and washed with 10 ml ice-cold 50 mM Tris-HCl, pH 7.4. Specific binding was determined by 10 μM apomorphine and radioactivity determined by counting in a LKB beta counter. Binding parameters were determined by non-linear least squares regression analysis, from which the inhibition constant K_i could be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of [^{3}H]-spiperone from the human dopamine D_4 receptor subtype of below 1.5 μM.

EXAMPLE 1

3-(4-(2-Phenylethyl)piperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole.

Sodium hydride (60% in oil, 35 g, 880 mmol) was added with care to a solution of 1-tetralone (54 g, 370 mmol), carbon disulfide (27 ml, 33.7 g, 443 mmol), and methyl iodide (52 ml, 115 g, 810 mmol) in THF (400 ml) at 0°C. The mixture was stirred at room temperature overnight, giving a yellow solution with a white precipitate. Saturated aqueous ammonium chloride solution and ethyl acetate were added, the mixture separated, and the organic layer washed with water and brine, dried ($MgSO_4$), evaporated *in vacuo*, and the resulting solid recrystallised from ethyl acetate / hexanes to give 2-(*bis*-methylthiomethylene)-4,5-dihydro-2H-naphthalen-1-one (67 g, 59%) as yellow cubes, m.p. 54-56°C; δ (360 MHz, $CDCl_3$) 2.43 (6 H, br s, Me), 2.98 (2 H, t, J = 6.7 Hz, CH_2), 3.26 (2 H, t, J = 6.7 Hz, CH_2), 7.22 (1 H, d, J = 7.6 Hz, H-5), 7.32 (1 H, t, J = 7.6 Hz, H-7), 7.43 (1 H, dt, J = 1.2 and 7.6 Hz, H-6), 8.10 (1 H, dd, J = 1.2 and 7.6 Hz, H-8).

2-(*Bis*-methylthiomethylene)-4,5-dihydro-2H-naphthalen-1-one (11.56 g, 46 mmol) and 1-*tert*-butyloxycarbonylpiperazine (10.3 g, 55 mmol) were refluxed in acetonitrile (300 ml) for 24 h. The mixture was cooled, water (500 ml) added, and extracted with ethyl acetate (3 x 200 ml). The combined organics were washed with water and brine, dried ($MgSO_4$), evaporated *in vacuo*, and the resulting oil purified by flash chromatography, eluting with dichloromethane then dichloromethane : methanol (97 : 3 v/v) to give 2-(methylthio[4-(*tert*-butyloxycarbonyl)-1-

piperazinyl]methylene)-4,5-dihydro-2H-naphthalen-1-one (8.75 g, 49%) as a foam; δ (360 MHz, $CDCl_3$) 1.49 (9H, s, ^tBu), 3.31 (3 H, s, MeS), 2.86-2.94 (4 H, m, CCH_2CH_2C), 3.3-3.5 (8 H, m, NCH_2CH_2N), 7.18 (1 H, d, J = 7.5 Hz, H-5), 7.30 (1 H, t, J = 7.5 Hz, H-7), 7.37 (1 H, dt, J = 1.4 and 7.5 Hz, H-6), 8.10 (1 H, dd, J = 1.4 and 7.5 Hz, H-8).

2-(Methylthio[4-(*tert*-butyloxycarbonyl)-1-piperazinyl]methylene)-4,5-dihydro-2H-naphthalen-1-one (5.3 g, 13.7 mmol) and hydrazine hydrate (3.4 g, 68.5 mmol) were stirred in ethanol (100 ml) at room temperature for 16 h. The solvent was evaporated *in vacuo*, and the resulting oil purified by flash chromatography, eluting with dichloromethane : methanol (95 : 5 v/v) to give 3-(4-(*tert*-butyloxycarbonylpiperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole (3.9 g, 80 %) as a yellow oil; δ (360 MHz, $CDCl_3$) 1.48 (9 H, s, ^tBu), 2.72 (2 H, t, J = 7.7 Hz, $CC\underline{H_2}CH_2C$), 2.95 (2 H, t, J = 7.7 Hz, $CCH_2C\underline{H_2}C$), 3.13 (4 H, t, J = 5.2 Hz, NCH_2), 3.53 (4 H, t, J = 5.2 Hz, NCH_2), 7.2-7.4 (4 H, m, ArH).

3-(4-(*tert*-Butyloxycarbonylpiperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole (1.65 g, 4.8 mmol) was dissolved in trifluoroacetic acid (10 ml). After 30 min the solvent was evaporated *in vacuo* to give 3-(piperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole *bis*-trifluoroacetate, which still contained an excess amount of trifluoroacetic acid (2.64 g), as a light brown solid; δ (360 Mhz, d_6-DMSO) 2.66 (2 H, t, J = 7.2 Hz, $CC\underline{H_2}CH_2C$), 2.95 (2 H, t, J = 7.2 Hz, $CCH_2C\underline{H_2}C$), 3.22 (4 H, br s, NCH_2), 3.30 (4 H, br s, NCH_2), 7.2-7.3 (3 H, m, ArH), 7.56 (1 H, d, J = 6.6 Hz, H-9), 8.8 (2H, br s, NH^+). This was used crude in the next reaction.

3-(Piperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole *bis*-trifluoroacetate (416 mg, 1.1 mmol), ethyldiisopropylamine (590 µl, 430 mg, 3.3 mmol), and 2-phenethyl bromide (168 µl, 228 mg, 1.23 mmol) were heated in DMF (3 ml) at 60 °C for 4 h. The mixture was cooled, diluted with water (20 ml), extracted with ethyl acetate (3 x 10 ml), the combined organic fractions washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The resulting light brown oil was dissolved in ethanol (2 ml), heated to boiling, and oxalic acid (1.3 ml of a 1M solution in ethanol) added. After cooling to room temperature the resulting solid was collected, washed with ethanol, and recrystallised from DMF : ethanol (1 :9 v/v) to give 3-(4-(2-phenylethyl)piperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole oxalate salt (98 mg, 30 % over two steps) as white needles mp 216-219 °C (Found: C, 66.55; H, 6.32; N, 12.30. $C_{23}H_{24}N_4$ $C_2O_4H_2$ requires C, 66.94; H, 6.29; N, 12.49%); δ (360 MHz, d_6-DMSO) 2.66 (2 H, t, J = 7.6 Hz, CCH_2CH_2C), 2.87 (2 H, t, J = 7.6 Hz, CCH_2CH_2C), 2.88 (2 H, t J = 7 Hz, $PhCH_2$), 3.1-3.2 (6H, m, CH_2), 3.25 - 3.4 (4 H, m, CH_2), 7.1-7.4 (8 H, m, ArH), 7.55 (1 H, d, J = 6.7 Hz, H-9); m/z (CI^+, NH_3) 359 ($M^+ + H$).

EXAMPLE 2

3-(4-Benzylpiperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole: oxalate salt, white microcrystalline solid, mp 254-256°C (from EtOH) (Found: C, 65.71; H, 6.04; N, 12.40. $C_{22}H_{24}N_4.C_2H_2O_4.0.25H_2O$ requires C, 65.66; H, 6.08; N, 12.76%); δ (360MHz, d_6-DMSO) 2.63 (2H, t, = 7.6Hz, CCH_2CH_2C), 2.86 (2H, t, J = 7.6Hz, CCH_2CH_2C), 2.96 (4H, br s, NCH_2), 3.26 (4H, br s, NCH_2), 4.04 (2H, s, $PhCH_2$), 7.1-7.3 (3H, m, ArH), 7.4-7.5 (5H, m, ArH), 7.54 (1H, d, J = 6.7Hz, H-9); m/z (CI+, NH_3) 345 (M^++H).

EXAMPLE 3

3-(4-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-piperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole

3-(Piperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole *bis*-trifluoroacetate (708mg, 2mmol), ethyldiisopropylamine (700µl, 511mg, 4mmol) and 3-dimethylaminomethyl-1H-pyrrolo[2,3-b]pyridine (175mg, 1mmol) were heated in toluene (4ml) and DMF (2ml) at 100°C for 3h. The mixture was cooled, water (20ml) added, and the mixture extracted with ethyl acetate (3 x 15ml). The combined organic extracts were washed with brine, dried and evaporated *in vacuo* to give a brown solid, which was suspended in boiling methanol (4ml), then cooled. The liquid was removed, and the solid recrystallised from aqueous methanol to give the title compound (53mg, 7%) as a white microcrystalline solid, mp 245-247°C (Found: C, 71.4; H, 6.35; N, 21.31. $C_{23}H_{24}N_6.0.25H_2O$ requires C, 71.02; H, 6.35; N, 21.60%); δ (360MHz, d_6-DMSO) 2.5-2.55 (4H, m, NCH_2), 2.61 (2H, t, J = 7.5Hz, CCH_2CH_2C), 2.84 (2H, t, J = 7.5Hz, CCH_2CH_2C), 3.05-3.10 (4H, m, NCH_2), 3.68 (2H, s, NCH_2C), 7.04 (1H, dd, J = 4.7 and 7.8Hz, NCHCH), 7.1-7.3 (3H, m, ArH), 7.37 (1H, s, CHNH), 7.52 (1H, d, J = 7.8Hz, CHCHCHN), 8.05 (1H, d, J = 6.6Hz, H-9), 8.19 (1H, d, J = 4.7Hz, NCHCH), 11.46 (1H, s, NH), 12.20 (1H, s, NH); m/z (CI^+, NH_3) 385 (M^++H).

EXAMPLE 4

3-(4-Benzylpiperazin-1-yl)-4,5-dihydronaphth[1,2-c]isoxazole

2-(Methylthio[4-(*tert*-butyloxycarbonyl)piperazin-1-yl]methylene)-4,5-dihydro-2H-naphthalen-1-one (70mg, 185μmol), hydroxylamine hydrochloride (139mg, 2mmol) and ethyldiisopropylamine (350μl, 256mg, 2mmol) were stirred in ethanol (2ml) for 16h. Water (10ml) was added, and the mixture extracted with ethyl acetate (3 x 10ml). The combined organic layers were washed with brine, dried, evaporated *in vacuo*, and purified by preparative thin layer chromatography to give 3-[3-(*tert*-Butyloxycarbonyl)piperazin-1-yl)-4,5-dihydronapth[1,2-c]isoxazole as a white solid (49mg, 77%); δ (360MHz, $CDCl_3$) 1.48 (9H, s, ^tBu), 2.78 (2H, t, J = 7.9Hz, $CC\underline{H}_2CH_2C$), 3.04 (2H, t, J = 7.9Hz, $CCH_2C\underline{H}_2C$), 3.29 (4H, t, J = 5.4Hz, NCH_2), 3.57 (4H, t, J = 5.4Hz, NCH_2), 7.2-7.3 (3H, m, ArH), 7.6-7.65 (1H, m, H-9). This was taken on in the same way as Example 1 to give the title compound as white cubes, mp 148-149°C (from ethyl acetate) (Found: C, 76.12; H, 6.61; N, 11.99. $C_{22}H_{23}NO$ requires C, 76.49; H, 6.71; N, 12.16%); δ (360MHz, d_6-DMSO) 2.45-2.50 (4H, m, NCH_2, partially under DMSO peak), 2.75 (2H, t, J = 7.5Hz, $CC\underline{H}_2CH_2C$), 2.99 (2H, t, J = 7.5Hz, $CCH_2C\underline{H}_2C$), 3.22 (4H, t, J = 4.8Hz, NCH_2), 3.52 (2H, s, NCH_2Ph), 7.2-7.4 (8H, m, ArH), 7.50 (1H, d, J = 7.6Hz, H-9); m/z (CI^+, NH_3) 346 ($\underline{M}^+$+H).

EXAMPLE 5

3-[4-(2-Phenylethyl)piperazin-1-yl]-4,5-dihydronaphth[1,2-c]isoxazole

Light brown crystals mp 134-136°C (from ethyl acetate/hexanes) (Found: C, 75.78; H, 6.84; N, 11.56. $C_{23}H_{25}N_3O.0.25H_2O$ requires C, 75.89; H, 7.06; N, 11.55%); δ (360MHz, d_6-DMSO) 2.55-2.60 (6H, m, CH_2's), 2.75-2.80 (4H, m, CH_2's), 2.99 (2H, t, J = 7.8Hz, CCH_2CH_2C), 3.23 (4H, t, J = 4.7Hz, NCH_2), 7.1-7.4 (8H, m, ArH), 7.50 (1H, dd, J = 2.1 and 6Hz, H-9), m/z (CI+, NH_3) 360 (M^++H).

EXAMPLE 6

3-[4-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)-piperazin-1-yl]-4,5-dihydronaphth[1,2-c]isoxazole

White plates, mp 248-250°C (from methanol) (Found: C, 71.26; H, 6.03; N, 17.81. $C_{23}H_{23}N_5O$ requires C, 71.66; H, 6.01; N, 18.17%); δ (360MHz, d_6-DMSO) 2.45-2.50 (4H, m, NCH_2, partially obscured by DMSO), 2.74 (2H, t, J = 7.8Hz, CCH_2CH_2C), 3.20 (4H, t, J = 4.4Hz, NCH_2), 3.69 (2H, s, NCH_2), 7.04 (1H, dd, J = 4.7 and 7.9Hz, CHCHN), 7.25-7.35 (3H, m, ArH), 7.37 (1H, s, CHNH), 7.50 (1H, d, J = 7.9Hz, CHCHCHN), 8.05 (1H, d, J = 6.6Hz, H-9), 8.20 (1H, d, J = 4.7Hz, CHCHN), 11.47 (1H, s, NH); m/z (CI+, NH_3) 386 (M^++H).

EXAMPLES 7 AND 8

3-(4-(2-Phenylethyl)piperazin-1-yl)-4,5-dihydro-2-methyl-2H-benzo[g]indazole and 3-(4-(2-Phenylethyl)piperazin-1-yl)-4,5-dihydro-1-methyl-1H-benzo[g]indazole

2-(Methylthio(4-(*tert*-butyloxycarbonyl)piperazin-1-yl)methylene-4,5-dihydro-2H-naphthalen-1-one (3.2g, 8.2mmol) and methylhydrazine (5ml) were kept in ethanol (30ml) for four days. Water (150ml) was added, and the mixture extracted with ethyl acetate (3 x 50ml). The combined organic layers were washed with brine, dried ($MgSO_4$), evaporated *in vacuo*, and purified by flash chromatography, eluting with hexane:ethyl acetate (4:1 v/v) to give 3-(4-(*tert*-butyloxycarbonyl)piperazin-1-yl)-4,5-dihydro-1-methyl-1H-benzo[g]indazole (342mg, 11%) as a colourless oil; ^{1}H NMR (360MHz, $CDCl_3$) δ 1.52 (9H, s, ^{t}Bu), 2.67 (2H, t, J = 7.3Hz, $CC\underline{H}_2CH_2C$), 2.94 (2H, t, J = 7.3Hz, $CCH_2C\underline{H}_2C$), 3.15 (4H, t, J = 5.1Hz, NCH_2), 3.61 (4H, t, J = 5.1Hz, NCH_2), 4.15 (3H, s, Me), 7.22-7.34 (3H, m, ArH), 7.55 (1H, d, J = 7.7Hz, H-9). Iradiation at δ 4.15 gave a positive nOe to the doublet at δ 7.55, and the reverse; and 3-(4-(*tert*-butyloxycarbonyl)piperazin-1-yl)-4,5-dihydro-2-methyl-2H-benzo[g]indazole (561mg, 19%) as a white solid δ (360MHz, $CDCl_3$) 1.54 (9H, s, ^{t}Bu), 2.86 (2H, t, J = 7.8Hz, $CC\underline{H}_2CH_2C$), 2.95 (2H, t, J = 7.8Hz, $CCH_2C\underline{H}_2C$), 3.08 (4H, t, J = 4.9Hz, NCH_2), 3.60 (4H, t, J = 4.9Hz, NCH_2), 7.20-7.30 (3H, m, ArH), 7.83 (1H, d, J = 7.5Hz, H-9).

These were taken on as for Example 1 to give 3-(4-(2-phenylethyl)piperazin-1-yl)-4,5-dihydro-2-methyl-2H-benzo[g]indazole oxalate salt, mp 244-245°C (from ethanol)

(Found: C, 66.94; H, 6.42; H, 11.71. $C_{24}H_{28}N_4.C_2H_2O_4.0.2H_2O$ requires C, 66.99; H, 6.57; N, 12.02%); δ (360MHz, d_6-DMSO) 2.8-2.9(4H, m, CCH_2CH_2C), 2.90-2.95 (2H, m, CH_2), 3.1-3.2 (6H, m, CH_2's), 3.2-3.25 (4H, m, CH_2's), 3.69 (3H, s, Me), 7.1-7.4 (8H, m, ArH), 7.61 (1H, d, J = 7.7Hz, H-9); m/z (CI^+, NH_3) 373 ($\underline{M}^+$+H), and 3-(4-(2-phenylethyl)piperazin-1-yl)-4,5-dihydro-1-methyl-1H-benzo[g]indazole oxalate salt, mp 225-226°C (from ethanol) (Found: C, 67.04; H, 6.66; N, 11.92. $C_{24}H_{28}N_4.C_2H_2O_4.0.2H_2O$ requires C, 66.99; H, 6.57; N, 12.01%); δ (360MHz, d_6-DMSO) 2.56 (2H, t, J = 7.7Hz, $CC\underline{H}_2CH_2C$), 2.83 (2H, t, J = 7.7Hz, $CCH_2C\underline{H}_2C$), 2.95 (2H, t, J = 8Hz, $PhCH_2$), 3.1-3.2 (6H, m, CH_2's), 3.25-3.35 (4H, m, CH_2's), 3.95 (3H, s, Me), 7.2-7.4 (8H, m, ArH), 7.63 (1H, d, J = 7.1Hz, H-9); m/z (CI^+, NH_3) 373 ($\underline{M}^+$+H).

EXAMPLE 9

3-(4-(2-Phenylethyl)piperazin-1-yl)-4,5-dihydro-1H-thieno[2,3-g]indazole

Oxalate salt, white plates, mp 145-147°C (from ethanol) (Found: C, 58.99; H, 5.73; N, 11.89. $C_{21}H_{24}N_4S.C_2H_2O_4.0.8H_2O$ requires C, 58.91; H, 5.93; N, 11.95%); δ (360MHz, d_6-DMSO) 2.76 (2H, t, J = 7.7Hz, CH_2), 2.9-3.0 (4H, m, CH_2's), 3.1-3.2 (6H, m, CH_2's), 3.2-3.3 (4H, m, CH_2's), 7.20-7.35 (6H, m, ArH), 7.39 (1H, d, J = 5.1Hz, ArH); m/z (CI^+, NH_3), 365 ($\underline{M}^+$+H).

EXAMPLE 10

3-(4-Benzylpiperazin-1-yl)-1,4-dihydroindeno[1,2-c]pyrazole

Off white crystals, mp 256-258°C (from DMF/Ether) (Found: C, 64.40; H, 5.57; N, 12.86. $C_{21}H_{22}N_4.C_2H_2O_4.0.5H_2O$ requires C, 64.32; H, 5.87; N, 13.05%) δ (360MHz, d_6-DMSO) 2.8-2.9 (4H, m, CH_2N), 3.3-3.4 (4H, m, CH_2N), 3.60 (2H, s, $ArCH_2$), 3.84 (2H, s, $ArCH_2N$), 7.23 (1H, t, J = 7.4Hz, ArH), 7.32 (1H, t, J = 7.4Hz, ArH), 7.36-7.52 (7H, m, ArH), m/z (CI^+, NH_3) 331 (M^++H).

EXAMPLE 11

3-(4-(2-Phenylethyl)piperazin-1-yl)-1,4-dihydroindeno[1,2-c]pyrazole

Oxalate salt, off white crystals, mp 212-214°C (from methanol/ether) (Found: C, 65.58; H, 6.04; N, 12.34. $C_{22}H_{24}N_4.1.1.C_2H_2O_4$ requires C, 66.54; H, 5.95; N, 12.63%) δ (360MHz, d_6-DMSO) 2.93-2.98 (2H, m, $ArCH_2CH_2$), 3.09-3.44 (6H, m, $ArCH_2CH_2$ and NCH_2), 3.4-3.5 (4H, m, NCH_2), 3.63 (2H, s, $ArCH_2Ar$), 7.21-7.35 (7H, m, ArH), 7.51 (2H, t, J = 7.2Hz, ArH m to CH_2CH_2) m/z (CI^+, NH_3) 345 (M^++H).

EXAMPLE 12

3-(4-Benzylpiperazin-1-yl)-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole

Oxalate salt, pale yellow crystals, mp 216-220°C (from ethanol) (Found: C, 63.09; H, 5.63; N, 11.74. $C_{22}H_{24}N_4.1.4.C_2H_2O_4$ requires C, 63.31; H, 5.74; N, 11.91%) δ (360MHz, d_6-DMSO) 2.86 (1H, br s, NCH_2CH_2), 3.32 (4H, br s,

$NCH_2C\underline{H}_2$), 3.58 (2H, s, $ArC\underline{H}_2C$), 3.90 (3H, s, $C\underline{H}_3$), 3.92 (2H, s, $ArC\underline{H}_2N$), 7.24-7.43 (7H, m, Ar$\underline{H}$), 7.50 (1H, d, J = 7.5Hz, Ar$\underline{H}$), 7.68 (1H, d, J = 7.5Hz, Ar$\underline{H}$) m/z (CI$^+$, NH_3) 345 ($\underline{M}^+$+H). Regiochemistry of Me group determined by NOE experiment carried out on an earlier intermediate.

EXAMPLE 13

3-(4-(1-Phenylethyl)piperazin-1-yl)-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole

Pale yellow crystals, mp 138-139°C (from ethanol) (Found: C, 76.87; H, 7.14; N, 15.47. $C_{23}H_{26}N_4$ requires C, 77.06; H, 7.31; N, 15.63%) δ (360MHz, d_6-DMSO), 2.53-2.58 (6H, m, $ArC\underline{H}_2CH_2$), 2.74-2.79 (2H, m, $ArCH_2C$), 3.19-3.22 (4H, m, $NCH_2C\underline{H}_2$), 3.59 (2H, s, $ArC\underline{H}_2C$), 3.89 (3H, s, $C\underline{H}_3$), 7.16-7.36 (7H, m, Ar$\underline{H}$), 7.49 (1H, d, J = 7.4Hz, ArH), 7.67 (1H, d, J = 7.4Hz, ArH) m/z (CI$^+$, NH_3) 359 ($\underline{M}^+$+H). Regiochemistry of Me group determined by NOE experiments carried out on an earlier intermediate.

EXAMPLE 14

3-(4-(1H-Pyrrolo[2,3-b]pyridin-3-ylmethyl)piperazin-1-yl)-1-methyl-4-dihydroindeno[1,2-c]pyrazole

Pale yellow needles, mp 235-240°C (from DMF) (Found: C, 70.85; H, 6.50; N, 21.61. $C_{23}H_{24}N_6.0.3H_2O$ requires C, 70.85; H, 6.36; N, 21.55%) δ (360MHz, d_6-DMSO) 2.49-2.51 (4H, m, $NC\underline{H}_2$), 3.2 (4H, brs, NCH_2), 3.56 (2H, s, $ArC\underline{H}_2$), 3.67 (2H, s, $ArCH_2$), 3.95 (3H, s, $C\underline{H}_3$), 7.04 (1H, dd, J = 7.8Hz and J = 4.7Hz, NCHC$\underline{H}$CH), 7.22 (1H, td, J = 7.5Hz and 1.1Hz, ArH), 7.34 (1H,

td, J = 7.5Hz and 1.1Hz, ArH), 7.38 (1H, d, J = 2.3Hz, NHCH), 7.48 (1H, d, J = 7.4Hz, ArH), 7.66 (1H, d, J = 7.4Hz, ArH), 8.05 (1H, dd, J = 7.8 and 1.3Hz, NCHCHCH), 8.20 (1H, dd, J = 4.7Hz and 1.5Hz, NCHCHCH), 11.4 (1H, br s, NH) m/z (CI^+, NH_3) 385 (M^++H). Regiochemistry of Me group determined by NOE experiment carried out on an earlier intermediate.

EXAMPLE 15

3-(1-(4-(2-Phenylethyl)piperazinyl))-4,5-dihydro-6,8-dimethyl-1H-benzo[g]indazole

Cream coloured needles, m.p. 177-179°C (from EtOH-Hexane) (Found: C, 76.9; H, 7.8; N, 14.2. $C_{25}H_{30}N_4 \cdot 0.2(H_2O)$ requires C, 77.0; H, 7.9; N, 14.4%). δ_H (360 MHz; $CDCl_3$) 2.29 (3H, s, ArMe), 2.30 (3H, s, ArMe), 2.65-2.77 (8H, m, 3 x NCH_2 and $ArCH_2$), 2.83-2.88 (4H, m, 2 x $ArCH_2$), 3.31 (4H, t, J=5Hz, 2 x NCH_2), 6.92 (1H, s, ArH), 7.06 (1H, broad s, ArH) and 7.18-7.31 (5H, m, Ph); m/z (CI^+; NH_3) 387 (M^++H).

EXAMPLE 16

3-(1-(4-(2-(3-Phenylpropyl))piperazinyl))-4,5-dihydro-1H-benzo[g]indazole

White amorphous solid, m.p. 170-172°C (from EtOH) (Found: C, 59.6; H, 5.9; N, 10.0. $C_{24}H_{28}N_4 \cdot 2(CO_2H)_2 \cdot 0.67(H_2O)$ requires C, 59.6; H, 6.0; N, 9.9%). δ_H (360 MHz; DMSO+CF_3CO_2H) 1.17 (3H, d, J=7Hz, $NCHCH_3$), 2.70-2.78 (3H, m, $NCHCH_3$ and $ArCH_2$), 2.95 (2H, t, J=7Hz, $ArCH_2$), 3.22-3.48 (4H, m, 2 x NCH_2), 3.56-3.90 (6H, m, 2 x NCH_2 and $ArCH_2$), 7.30-7.40 (8H, m, 8 of ArH), 7.64 (1H, d, J=6Hz, 1 of ArH) and 9.90 (1H, broad s, NH); m/z (CI^+; NH_3) 390 (M^++NH_4), 373 (M^++H).

EXAMPLE 17

3-(4-(2-Phenylethyl)piperazin-1-yl)-1,4,5,6-tetrahydro-1,2-diazabenzo[e]azulene

White needles, m.p. 147-148°C (from ethyl acetate : hexane) (Found: C, 76.56; H, 7.62; N, 14.80. $C_{24}H_{28}N_4 \cdot 0.2(H_2O)$ requires C, 76.64; H, 7.61; N, 14.90).

δ (360 MHz; δ_6-DMSO) 1.89 (2H, quintet, J=5Hz, $CH_2C\underline{H}_2CH_2$), 2.55-2.7 (10H, m, $C\underline{H}_2$'s), 2.76-2.82 (2H, m, $C\underline{H}_2$), 3.00-3.05 (2H, m, CH_2), 3.25-3.35 (2H, m, CH_2), 7.1-7.25 (8H, m, ArH), 7.69 (1H, d, J=7Hz, H-10), 12.1 (1H, s, NH); m/z (CI^+; NH_3) 373 (M^++H).

EXAMPLE 18

1-Ethyl-3-(4-(2-phenylethyl)piperazin-1-yl)-4,5-dihydrobenzo[g]indazole

Oxalate salt, white solid, m.p. 193-195°C (from ethanol) (Found: C, 66.91; H, 6.49; N, 10.98. $C_{25}H_{30}N_4 \cdot 1.2(C_2H_2O_4)$ requires C, 66.54; H, 6.60; N, 11.33%). δ_H (360 MHz; δ_6-DMSO) 1.35 (3H, t, J=7.2Hz, CH_3), 2.58-2.64 (2H, m, CH_2), 2.80-2.90 (2H, m, CH_2), 2.95-3.00 (2H, m, CH_2), 3.1-3.4 (10H, m, CH_2's), 4.28 (2H, q, J=7.2Hz, $C\underline{H}_2CH_3$), 7.2-7.4 (8H, m, ArH), 7.51 (1H, d, J=7.8Hz, ArH-9); irradiation of the signal at 4.28 gives a positive nOe to the signal at 7.51 ppm; m/z (CI^+; NH_3) 387 (M^++H).

EXAMPLE 19

3-(4-(2-(5-Methylfuran-2-yl)ethyl)piperazin-1-yl)-4,5-dihydrobenzo[g]indazole

5-methyl furan-2-acetic acid

To a solution of potassium cyanide (12.2g, 0.187mol) and sodium carbonate (36g, 0.338mol) in water (250ml) was added 5-methyl furfural (7.5ml, 75mmol) in 1,4-dioxane (12ml) followed by glyoxal busulphite (3.0g, 0.289mol) and water (240ml). After stirring for 2½hr at room temperature, the reaction was worked up by adding 5N $HCl_{(aq)}$ to the reaction mixture carefully (HCN↑) until the pH fell to ≈1-2. Stirring was continued for 1hr after which time, no more gas was evolved.

Products were extracted with chloroform (3 x 150ml). Combined organics were washed with brine before being dried over Na_2SO_4 and concentrated in vacuo.

A brown solid was afforded (8.1g, 78%). δ_H (250 MHz, $CDCl_3$), 2.26 (3H, s, $ArC\underline{H}_3$), 3.66 (2H, s, $ArC\underline{H}_2$), 5.90 (1H, d, J=5Hz, Ar$\underline{H}$), 6.12 (1H, d, J=5Hz, Ar$\underline{H}$).

3-(4-(5-methylfuranyl)acetylpiperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole

To a solution of 3-piperazin-1-yl-4,5-dihydro-1H-benzo[g]indazole bistrifluoroacetate (450mg, 0.94mmol) and Hünigs base (664μl, 3.76mmol) in dichloromethane (25ml), was added 5-methylfuranyl-2-acetic acid (131mg, 0.94mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (200mg, 1.04mmol) and hydroxybenzotriazole (140mg, 1.04mmol). The reaction was stirred for 4hr at room temperature under nitrogen. The reaction mixture was poured into sodium bicarbonate solution and extracted with ethyl acetate (2 x 50ml). The combined organics were washed with water and brine before being dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed through silica eluting with 5% MeOH/DCM/1% $NH_{3(aq)}$ (v/v) to give the title compound as a pale brown crystalline solid (180mg, 51%). δH (250 MHz, d_6-DMSO), 2.24 (3H, s, $ArC\underline{H}_3$), 2.65 (2H, t, J=3.8Hz, $CC\underline{H}_2CH_2C$), 2.65 (2H, t, J=3.8Hz, $CCH_2C\underline{H}_2C$), 3.05 (4H,br s, $N\underline{C}H_2CH_2N$), 3.64 (4H, br s, $NCH_2C\underline{H}_2N$), 3.74 (2H, s, $ArC\underline{H}_2C$), 5.98 (1H, d, J=5Hz, Ar$C\underline{H}$), 6.06 (1H, d, J=5Hz, Ar$\underline{H}$), 7.14-7.33 (3H, m, Ar$\underline{H}$), 7.52 (1H, d, J=7.0Hz, Ar$\underline{H}$), 12.40 (1H, br s, N$\underline{H}$).

3-(4-(2-(5-Methylfuran-2-yl)ethyl)piperazin-1-yl)-4,5-dihydrobenzo[g]indazole

To a solution of 3-(4-(5-methylfuranyl)acetyl piperazin-1-yl)4,5-dihydro-1H-benzo[g]indazole (170mg), 0.45mmol) in tetrahydrofuran (25ml) was added $LiAlH_4$ (1.0M in THF) (680µl, 0.68mmol) slowly at room temperature under N_2. Stirring was continued for 1hr.

Reaction mixture was worked up by cautious addition of 20% $NaOH_{(aq)}$ until no further gas was evolved. More water was then added (30ml) and the mixture extracted with ethyl acetate (2 x 50ml). Combined organics were washed with water and brine before being dried over Na_2SO_4 and concentrated in vacuo. The oily residue was chromatographed on silica preparative TLC plates eluting with 4% MeOH/DCM/1% $NH_{(aq)}$ (v/v) to give purified title compound. (104 mg,≈99%) as pale yellow crystals, m.p. 150-152°C (Found; C, 71.95; H, 7.37; N, 15.01. $C_{22}H_{26}N_4O \cdot 0.3(H_2O)$ requires C, 71.83; H, 7.29; N, 15.23%); δH (360 MHz, d_6-DMSO), 2.21 (3H, s, $OCCH_3$), 2.44-2.66 (4H, m, CH_2), 2.74 (2H, tr, J=7.4Hz, CH_2), 2.86 (2H, t, J=7.4Hz, CH_2), 3.08 (4H, br s, NCH_2), 5.93 (1H, s, OCCH), 5.98 (1H, s, OCCH), 7.15-7.27 (3H, m, ArH), 7.52 (1H, br d, J=7.0Hz, ArH), 12.23 (1H, br s, NH) m/z (CI^+, NH_3) 363 (M^++H).

EXAMPLE 20

2-Methyl-3-(4-(2-phenylethyl)piperazin-1-yl)-4,5,6-tetrahydro-1,2-diazabenzo[e]azulene

Oxalate salt, white crystals, m.p. 225-228°C (from ethanol) (Found; C, 68.28; H, 6.73; N, 11.61. $C_{25}H_{30}N_4 \cdot (COOH)_2$ requires C, 68.05; H, 6.77; N, 11.76%); δH (360 MHz, d_6-DMSO), 1.94 (2H, m, $CH_2CH_2CH_2$), 2.75 (4H, m, CH_2), 2.94 (2H, m, CH_2), 3.10 (6H, m, CH_2), 3.27 (4H, br s, CH_2), 3.72 (3H, s, NCH_3), 7.14-7.36 (8H, m, ArH), 7.87 (1H, d, J=7.3Hz, ArH) m/z (CI^+, NH_3) 387 (M^++H).

EXAMPLE 21

3-(4-(2-(2-Chlorophenyl)ethyl)piperazin-1-yl)-4,5-dihydrobenzo[g]indazole

Oxalate salt, pale yellow hexagonal plates, m.p. 134-136°C (from ethanol) (Found; C, 61.58; H, 5.61; N, 11.33. $C_{23}H_{25}N_4Cl \cdot (COOH)_2 \cdot 0.2\ H_2O$ requires C, 61.71; H, 5.68; N, 11.51%); δH (360 MHz, d_6-DMSO), 2.66 (2H, t, J=8.0Hz, CH_2), 2.88 (2H, t, J=8.0Hz, CH_2), 3.03-3.07 (8H, m, CH_2), 3.27 (4H, br s, CH_2), 7.19-7.47 (7H, m, ArH), 7.55 (1H, d, J=6.5, ArH) m/z (CI^+, NH_3) 393 (M^++H).

EXAMPLE 22

3-(4-(1,2,3,4-Tetrahydronaphthy-2-yl)piperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole

Oxalate salt, pale pink crystals, m.p. 208-210°C (from ethanol) (Found; C, 61.39; H, 5.72; N, 10.26. $C_{25}H_{28}N_4 \cdot 2(COOH)_2$ requires C, 61.69; H, 5.71; N, 9.92%); δH (360 MHz, d_6-DMSO), 1.78-1.80 (1H, m, CH_AH_B), 2.31 (1H, br s, CH_AH_B), 2.67 (2H, t, J=7.2Hz, CH_2), 2.83-3.07 (5H, m, CH_2), 3.17-3.20 (1H, m, CH), 3.39-3.57 (9H, m, CH_2), 7.15-7.30 (7H, m, ArH), 7.56 (1H, d, J=7.2Hz, ArH) m/z (CI^+, NH_3) 385 (M^++H).

EXAMPLE 23

4-(4-Benzylpiperazin-1-yl)-5H-indeno[1,2-d]pyrimidin-2-ylamine

To dry isopropyl alcohol (10ml) was added sodium metal (154mg, 6.7mmol) and the mixture refluxed under N_2 until all of the sodium had dissolved (≈ 0.5h). To this solution was then added guanidine hydrochloride (64.3ml, 6.7mmol) and the suspension refluxed for a further 0.5h. Meanwhile, 2-(methylthio[4-(*tert*-butyloxycarbonyl)-1-piperazinyl)methylene-indan-1-one (500mg, 1.34mmol) was dissolved in isopropylalcohol (3ml) and after 0.5h was added, in solution, to the refluxing suspension. The reaction was refluxed for 4h and then stirred at room temperature for 16h. Work-up of the reaction was performed by pouring the mixture into saturated sodium bicarbonate solution (150ml) and extracting the products into ethyl acetate (2 x 50ml). The organic layer was then separated and washed with water and brine before being dried over Na_2SO_4 and concentrated *in vacuo*. The residues were chromatographed upon flash silica eluting with dichloromethane:methanol (95:5 v/v) to give a pale yellow foam, δ (250MHz, $CDCl_3$) 1.50 (9H, s, $C(C\underline{H}_3)_3$), 3.52-3.58 (4H, m, $NC\underline{H}_2$), 3.80-3.86 (4H, m, $NC\underline{H}_2$), 3.90 (2H, s, $ArC\underline{H}_2$), 4.8 (2H, br s, $N\underline{H}_2$), 7.44-7.48 (2H, m, Ar<u>H</u>), 7.55-7.58 (1H, m, Ar<u>H</u>), 7.98-8.02 (1H, m, Ar<u>H</u>). This was deprotected with trifluoroacetic acid and then N-benzylated with benzyl bromide to give the title compound as pale yellow crystals, mp 175-180°C (from ethanol) (Found: C, 70.74; H, 6.28; N, 18.46. $C_{22}H_{23}N_5.0.8H_2O$ requires C, 71.06; H, 6.67; N, 18.83%) δ (360MHz, 353K, d_6-DMSO) 2.53 (4H, m, $NC\underline{H}_2C\underline{H}_2$), 3.56 (2H, s, $ArC\underline{H}_2C$), 3.80 (4H, $NCH_2C\underline{H}_2$), 3.93 (2H, s, $ArC\underline{H}_2N$), 5.8 (2H, br s, $N\underline{H}_2$), 7.25-7.44 (7H, m, Ar<u>H</u>), 7.55 (1H, d, J = 6.7Hz, Ar<u>H</u>), 7.78 (1H, d, J = 7.6Hz, Ar<u>H</u>) m/z (CI^+, NH_3) 358 ($\underline{M}^+$+H).

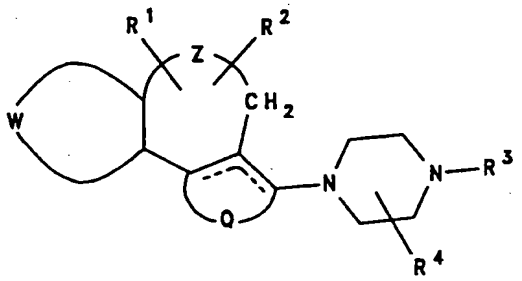
EXAMPLE 24

4-(4-(2-Phenylethyl)piperazin-1-yl)-5H-indeno[1,2-d]pyrimidin-2-ylamine

Pale yellow crystals, mp 122-124°C (from ethanol) (Found: C, 73.57; H, 6.60; N, 18.49. $C_{23}H_{25}N_5.0.8H_2O$ requires C, 73.65; H, 6.82; N, 18.67%) δ_H (360MHz, d_6-DMSO) 2.51-2.59 (6H, m, $ArCH_2CH_2$ and NCH_2CH_2), 2.76-2.80 (2H, m, $ArCH_2CH_2N$), 3.76-3.79 (4H, m, NCH_2CH_2), 3.96 (3H, s, $ArCH_2C$), 6.04 (2H, br s, NH_2), 7.16-7.31 (5H, m, ArH), 7.38-7.46 (2H, m, ArH), 7.57 (1H, d, J = 6.5Hz, ArH), 7.75 (1H, dd, J = 6.6Hz and 2.1Hz, ArH) m/z (CI^+, NH_3) 327 (M^++H).

CLAIMS:

1. A compound of formula I, or a salt thereof or a prodrug thereof:



(I)

wherein the broken line represents a double bond whereby the heteroaromatic ring containing Q is aromatic;

W represents the residue of an optionally substituted aromatic or heteroaromatic ring;

Q represents the residue of a heteroaromatic ring selected from $=N-NR^5-$, $-NR^5-N=$, $=N-O-$, $-O-N=$ and $=N-CR^6=N-$;

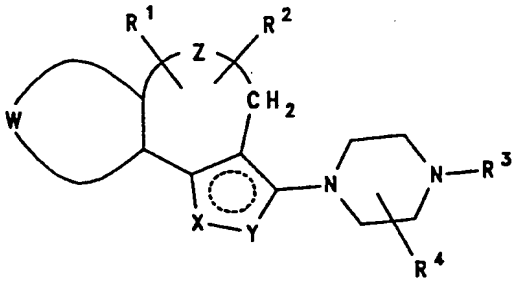
Z represents a chemical bond, an oxygen or sulphur atom, or a methylene or ethylene group;

R^1, R^2 and R^5 independently represent hydrogen or C_{1-6} alkyl;

one of R^3 and R^4 represents hydrocarbon or a heterocyclic group, and the other of R^3 and R^4 represents hydrogen, hydrocarbon or a heterocyclic group; and

R^6 represents C_{1-6}alkyl or $-NR^aR^b$, in which R^a and R^b independently represent hydrogen or C_{1-6}alkyl.

2. A compound as claimed in claim 1 represented by formula (IA), and salts and prodrugs thereof:



(IA)

wherein the broken circle represents two non-adjacent double bonds whereby the five-membered ring containing X and Y is aromatic;

W represents the residue of an optionally substituted aromatic or heteroaromatic ring;

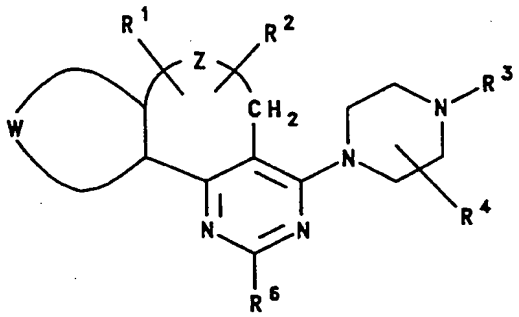
one of X and Y represents nitrogen, and the other of X and Y represents oxygen or N-R^5;

Z represents a chemical bond, an oxygen or sulphur atom, or a methylene or ethylene group;

R^1, R^2 and R^5 independently represent hydrogen or C_{1-6} alkyl; and

one of R^3 and R^4 represents hydrocarbon or a heterocyclic group, and the other of R^3 and R^4 represents hydrogen, hydrocarbon or a heterocyclic group.

3. A compounds as claimed in claim 1 represented by formula (IB), and salts and prodrugs thereof:



(IB)

wherein

W represents the residue of an optionally substituted aromatic or heteroaromatic ring;

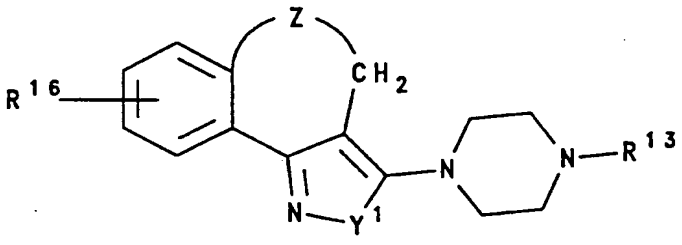
Z represents a chemical bond, an oxygen or sulphur atom, or a methylene or ethylene group;

R^1 and R^2 independently represent hydrogen or C_{1-6} alkyl;

one of R^3 and R^4 represents hydrocarbon or a heterocyclic group, and the other of R^3 and R^4 represents hydrogen, hydrocarbon or a heterocyclic group; and

R^6 represents C_{1-6} alkyl or $-NR^aR^b$, in which R^a and R^b independently represent hydrogen or C_{1-6} alkyl.

4. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

Z is as defined in claim 1;

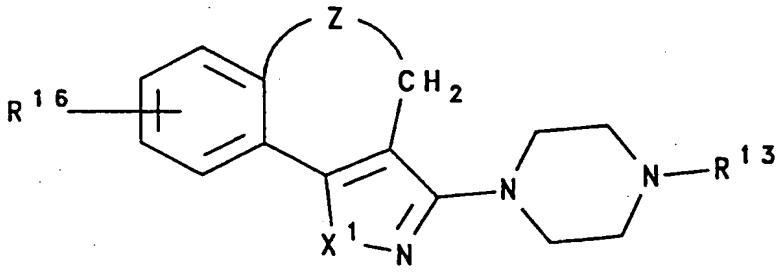
Y^1 represents oxygen or N-R^{15};

R^{13} represents C_{2-6} alkenyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted;

R^{15} represents hydrogen or C_{1-6} alkyl; and

R^{16} represents hydrogen, halogen, trifluoromethyl, cyano, nitro, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or C_{2-6} alkylcarbonyl.

5. A compound as claimed in claim 1 represented by formula IIB, and salts and prodrugs thereof:



(IIB)

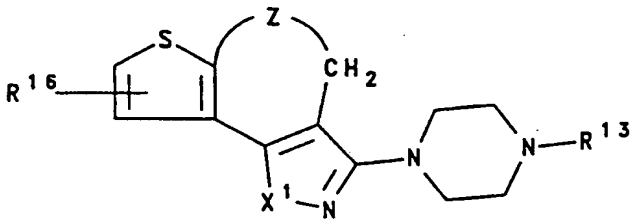
wherein

X^1 represents oxygen or N-R^{15};

Z is as defined in claim 1; and

R^{13}, R^{15} and R^{16} are as defined in claim 4.

6. A compound as claimed in claim 1 represented by formula IIC, and salts and prodrugs thereof:



(IIC)

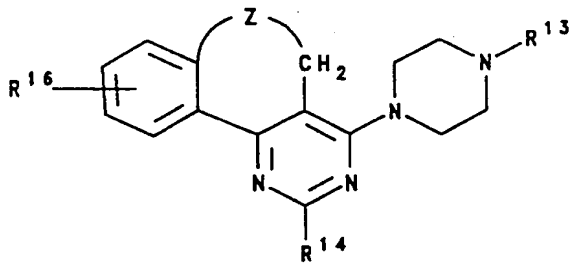
wherein

Z is as defined in claim 1;

R^{13} and R^{16} are as defined in claim 4; and

X^1 is as defined in claim 5.

7. A compound as claimed in claim 1 represented by formula IID, and salts and prodrugs thereof:



(IID)

wherein

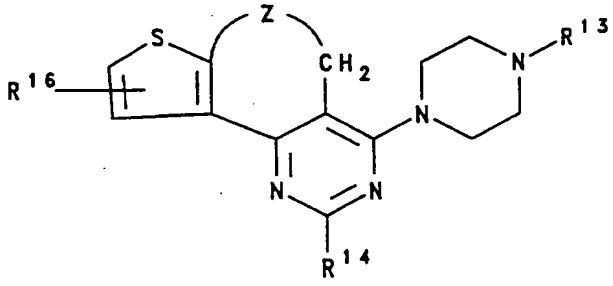
Z is as defined in claim 1;

R^{13} represents C_{2-6} alkenyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted;

R^{14} represents C_{1-6} alkyl, amino, C_{1-6} alkylamino or di(C_{1-6})alkylamino; and

R^{16} represents hydrogen, halogen, trifluoromethyl, cyano, nitro, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or C_{2-6} alkylcarbonyl.

8. A compound as claimed in claim 1 represented by formula IIE, and salts and prodrugs thereof:



(IIE)

wherein

Z is as defined in claimm 1; and

R^{13}, R^{14} and R^{16} are as defined in claim 7.

9. A compound selected from:

3-[4-(2-phenylethyl)piperazin-1-yl]-4,5-dihydro-1H-benzo[g]indazole;

3-(4-benzylpiperazin-1-yl)-4,5-dihydro-1H-benzo[g]indazole;

3-[4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)piperazin-1-yl]-4,5-dihydro-1H-benzo[g]indazole;

3-(4-benzylpiperazin-1-yl)-4,5-dihydronaphth[1,2-c]-isoxazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-4,5-dihydronaphth[1,2-c]isoxazole;

3-[4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)piperazin-1-yl]-4,5-dihydronaphth[1,2-c]isoxazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-4,5-dihydro-2-methyl-2H-benzo[g]indazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-4,5-dihydro-1-methyl-1H-benzo[g]indazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-4,5-dihydro-1H-thieno[2,3-g]indazole;

3-(4-benzylpiperazin-1-yl)-1,4-dihydroindeno[1,2-c]pyrazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-1,4-dihydroindeno[1,2-c]pyrazole;

3-(4-benzylpiperazin-1-yl)-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole;

3-[4-(2-phenylethyl)piperazin-1-yl]-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole;

3-[4-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)piperazin-1-yl]-1-methyl-1,4-dihydroindeno[1,2-c]pyrazole;

4-(4-benzylpiperazin-1-yl)-5H-indeno[1,2-d]pyrimidin-2-ylamine;

4-[4-(2-phenylethyl)piperazin-1-yl]-5H-indeno[1,2-d]pyrimidin-2-ylamine;
and salts and prodrugs thereof.

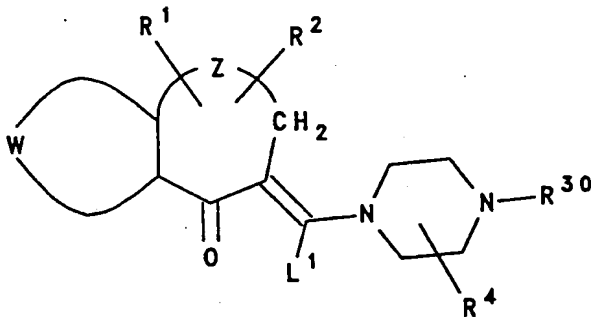
10. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier.

11. A compound as claimed in any one of claims 1 to 9 for use in therapy.

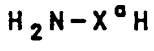
12. The use of a compound as claimed in any one of claims 1 to 9 for the manufacture of a medicament for the treatment and/or prevention of disorders of the dopamine system.

13. A method for the treatment and/or prevention of disorders of the dopamine system, which method comprises administering to a patient in need of such treatment an effective amount of a compound as claimed in any one of claims 1 to 9.

14. A process for the preparation of a compound as claimed in claim 1, wherein Q represents $=N-NR^5-$, $-NR^5-N=$, $=N-O-$ or $-O-N=$, which comprises reacting a compound of formula III with a compound of formula IVa:



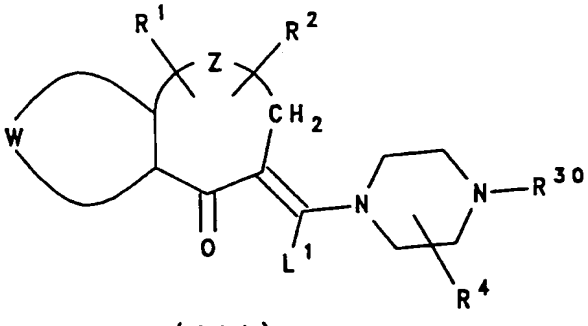
(III)



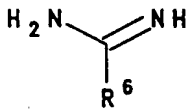
(IVa)

wherein W, Z, R^1, R^2 and R^4 are as defined in claim 1, R^{30} corresponds to the group R^3 as defined in claim 1 or represents an amino-protecting group, X^a represents oxygen or N-R^5 in which R^5 is as defined in claim 1, and L^1 represents a suitable leaving group; followed, where necessary, by removal of the amino-protecting group R^{30}; and followed, if necessary, by separation of the resulting mixture of isomers; and subsequently, if desired, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

15. A process for the preparation of a compound as claimed in claim 1, wherein Q represents =N-CR^6=N-, which comprises reacting a compound of formula III with a compound of formula IVb:



(III)



(IVb)

wherein W, Z, R^1, R^2, R^4 and R^6 are as defined in claim 1, R^{30} corresponds to the group R^3 as defined claim 1 or represents an amino-protecting group, and L^1 represents a suitable leaving group; in the presence of a base; followed, where necessary, by removal of the amino-protecting group R^{30}; and subsequently, if desired, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/GB 94/01936

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/54 C07D261/20 C07D239/70 C07D471/04 C07D495/04
C07D405/12 A61K31/42 A61K31/415 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 384 228 (DAINIPPON PHARMACEUTICAL CO., LTD.) 29 August 1990 see the whole document ---	1-15
X,P	WO,A,94 10162 (MERCK SHARP & DOHME LIMITED) 11 May 1994 see the whole document ---	1-15
A	EP,A,0 494 817 (ADIR ET COMPAGNIE) 15 July 1992 see the whole document ---	1-15
A	EP,A,0 402 644 (HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED) 19 December 1990 see claims; examples -----	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 1994	-4. 01. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int[redacted]pplication No.
PCT/GB94/01936

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 13 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0384228	29-08-90	AU-B-	622976	30-04-92
		AU-A-	4912290	30-08-90
		EP-A-	0484988	13-05-92
		JP-A-	2289551	29-11-90
		US-A-	5041443	20-08-91
		US-A-	5185338	09-02-93
WO-A-9410162	11-05-94	AU-B-	5341394	24-05-94
EP-A-0494817	15-07-92	FR-A-	2671350	10-07-92
		AU-B-	642570	21-10-93
		AU-A-	1006592	16-07-92
		CA-A-	2058878	09-07-92
		JP-A-	4308584	30-10-92
		US-A-	5173490	22-12-92
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		AU-A-	5577090	22-11-90
		CA-A-	2017193	19-11-90
		CN-A-	1048037	26-12-90
		IL-A-	94425	27-02-94
		JP-A-	3063263	19-03-91
		JP-B-	6062580	17-08-94
		PL-B-	163965	31-05-94
		US-A-	5364866	15-11-94